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PERSPECTIVES

O_2 sensing in chromaffin cells: new duties for T-type channels

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T-type Cav3 channels are voltage-gated Ca^{2+} channels that are able to sustain key physiological functions such as low-threshold spikes generation, neuronal and cardiac pacemaking, muscle contraction, hormone release, cell growth and differentiation. This mainly derives from the unique property of T-type channels that activate at rather negative voltages (~ -60 mV). These channels are ubiquitous in most excitable tissues and their expression at sufficient densities lowers the threshold of action potential generation with a consequent increase of cell excitability. The chromaffin cells of adult adrenal medulla seemed to escape this general rule, but recent works have shown that during chronic hypoxia or under β-adrenergic stimulation, chromaffin cells also acquire sufficiently high densities of Cav3.2 T-type channels, which lower the resting membrane potential and sustain low-threshold spike activity (Carbone *et al.* 2006; Carabelli *et al.* 2007). Recruitment of T-type channels is not a unique feature of chromaffin cells. PC12 cells also express Cav3.2 channels during exposure to chronic hypoxia, the effect being mediated by hypoxia-inducible factors (HIFs) (Del Toro *et al.* 2003).

An intriguing question is why chromaffin cells should recruit new T-type channels during chronic hypoxia when they are already well equipped with high- (N, P/Q) and mid-threshold (L and R) Ca^{2+} channel types that control chromaffin cell firing activity and catecholamine secretion. An easy answer is that T-type channel availability increases cell excitability and broadens the range of membrane voltage at which adrenaline and noradrenaline are secreted, assuming that T-type channels are coupled to exocytosis with the same efficacy as other voltage-gated Ca^{2+} channels. Indeed, Cav3.2 channels are effectively coupled to secretion with the same Ca^{2+} efficacy of L-, N-, P/Q- and R-type channels (Giancippoli *et al.* 2006), thus proving that T-types do not only participate in lowering the threshold of cell excitability but also contribute to exocytosis (and possibly to endocytosis) in adult chromaffin cells. This newly uncovered duty of T-type channels opens a further critical question. Are the Cav3.2 channels available only during pathological states of adrenal chromaffin cells (chronic hypoxia, intense β-adrenergic stimulation, etc.) or do they serve some key physiological role during adrenal medulla development and maturation?

The paper by Levitsky & López-Barneo (2009) that appears in this issue of *The Journal of Physiology* furnishes a full answer to this question and proves, in a very elegant way, that T-type channels are indeed functionally expressed in neonatal rat chromaffin cells and help in sensing acute-hypoxia conditions. At the early developmental stage, the adrenal medulla acts as an O_2 sensor (Seidler & Slotkin, 1985), responding to acute hypoxia by releasing adequate amounts of catecholamines, which critically regulate neonatal survival and adaptation to extra-uterine life. Catecholamines stimulate cardiac activity and prepare the lungs for air breathing. Levitsky & López-Barneo clearly show that neonatal rat chromaffin cells respond to acute hypoxia with an increased rate of catecholamine secretion that is strongly attenuated by the same Ni^{2+} concentration that reversibly blocks Cav3.2 channels. Since T-type channels in chromaffin cells open by mild membrane depolarization (Carabelli *et al.* 2007), it is likely that acute hypoxia causes the fast closing of K^+ channels and subsequent openings of T-type channels. Ca^{2+} entry through these channels causes the acute hypoxia-evoked secretion of catecholamines.

The paper also shows that when O_2 sensing disappears in adult chromaffin cells following splanchnic innervation, the expression of functioning T-type channels is also switched off, to reappear again with the O_2 sensitivity when the adult adrenal medulla is artificially denervated. Thus, T-type channels and O_2 sensing appear critically linked in the absence of the sympathetic neurogenic control of chromaffin cell activity. The work highlights the relevant role that T-type channels play in the control of Ca^{2+}-dependent exocytosis evoked by acute hypoxia in neonatal chromaffin cells and opens new interesting issues concerning the mechanisms by which a cell up-regulates the levels of low-threshold Ca^{2+} channels during the fetal stage or down-regulates during cell maturation. An open issue is the role that cholinergic innervation plays in these processes, possibly through a Ca^{2+}-driven mechanism which is probably activated by an increased Ca^{2+} entry through open nicotinic receptors (nAChRs). A second open issue is the possibility that other voltage-gated Ca^{2+} channels may contribute to O_2 sensing in neonatal chromaffin cells, as this possibility has not been fully investigated in the present work.

The findings by Levitsky and López-Barneo have great physiological relevance and might also have important pathophysiological implications. For instance, T-type channel down-regulation in chromaffin cells might be one of the causes of sudden infant death syndrome (SIDS), a disorder associated with decreased chemoreceptor excitability. Clinical studies suggest that cigarette smoking is one of the major risk factors for SIDS. Chronic nicotine *in utero* suppresses the sensitivity of chromaffin cells to hypoxia by favouring fetal and postnatal death (Buttgieg *et al.* 2008). Through the activation of nAChRs, nicotine in fetal blood might act as a wrong stimulus of premature adrenal medulla innervations with consequent down-regulation of functioning T-type channels. In this way, nicotine-evoked suppression to acute hypoxia may directly derive from an abnormally low T-type channel expression in neonatal chromaffin cells.

Obviously, the molecular mechanisms by which T-type channels control catecholamine secretion and O_2 sensing require further investigation. They are of great interest in light of the possible adverse effects that any malfunctioning of the sympathoadrenal system might have on the overall body function.

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